PATENT COOPERAT N TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 November 2000 (14.11.00)	
International application No. PCT/EP00/02467	**Applicant's or agent's file reference** ML/B45182
International filing date (day/month/year) 17 March 2000 (17.03.00)	**Priority date** (day/month/year) 19 March 1999 (19.03.99)
Applicant CAPIAU, Carine et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 October 2000 (13.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2000 (28.09.2000)

PCT

(10) International Publication Number
WO 00/56359 A3

(51) International Patent Classification[7]: A61K 39/09, 39/385, 39/39, A61P 31/04

(21) International Application Number: PCT/EP00/02467

(22) International Filing Date: 17 March 2000 (17.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9906437.0	19 March 1999 (19.03.1999)	GB
9909077.1	20 April 1999 (20.04.1999)	GB
9909466.6	23 April 1999 (23.04.1999)	GB
9916677.9	15 July 1999 (15.07.1999)	GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM BIOLOGICALS S.A.** [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAPIAU, Carine** [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE). **DESCHAMPS, Marguerite** [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE). **DESMONS, Pierre, Michel** [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE). **LAFERRIERE, Craig, Antony, Joseph** [CA/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE). **POOLMAN, Jan** [NL/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE). **PRIEELS, Jean-Paul** [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B-1330 Rixensart (BE).

(74) Agent: **GIDDINGS, Peter, John**; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
1 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/56359 A3

(54) Title: VACCINE AGAINST STREPTOCOCCUS PNEUMONIAE

(57) Abstract: The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to vaccines comprising a pneumococcal polysaccharide antigen, typically a pneumococcal polysaccharide conjugate antigen, formulated with a protein antigen form *Streptococcus pneumoniae*, and optionally a Th1-inducing adjuvant.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/02467

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/09 A61K39/385 A61K39/39 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 06951 A (PATON JAMES CLELAND ;HANSMAN DAVID JOHN (AU); MITCHELL TIMOTHY JOH) 28 June 1990 (1990-06-28) cited in the application page 3, line 35 -page 4, line 23 page 10, line 1 - line 3	1-9, 13-18
Y	claims 1-14 ---	10-12
X	LEE C J ET AL: "Immunologic epitope, gene, and immunity involved in pneumococcal glycoconjugate." CRITICAL REVIEWS IN MICROBIOLOGY, vol. 23, no. 2, 1997, pages 121-141, XP000946772	1-7, 13-18
Y	the whole document, especially page 132 column 2 line 27 - page 135 column 2 line 18 --- -/--	8-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	30/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stein, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BRILES DAVID E ET AL: "Pneumococcal diversity: Considerations for new vaccine strategies with emphasis on pneumococcal surface protein A (PspA)." CLINICAL MICROBIOLOGY REVIEWS, vol. 11, no. 4, October 1998 (1998-10), pages 645-657, XP000946754 ISSN: 0893-8512	1-7, 13-18
Y	the whole document especially page 646 column 1 line 35 - page 646 column 2 line 9; page 653 column 1 line 27-46	8-12

Y	WO 96 33739 A (SMITHKLINE BEECHAM BIOLOG ;GARCON NATHALIE MARIE JOSEPHE (BE); FRI) 31 October 1996 (1996-10-31) cited in the application page 1, line 1 -page 3, line 21 claims 1,5,8-10,12	8-12

X	ALEXANDER JANET E ET AL: "Immunization of Mice with Pneumolysin Toxoid Confers a Significant Degree of Protection against At Least Nine Serotypes of Streptococcus pneumoniae." INFECTION AND IMMUNITY, vol. 62, no. 12, 1994, pages 5683-5688, XP002149967 ISSN: 0019-9567 page 5683, column 1, line 26 -column 2, line 8 page 5687, column 1, line 51 - line 58	1-5, 13-18

A	MICHON F ET AL: "Multivalent pneumococal capsular polysaccharide conjugate vaccines employing genetically detoxified pneumolysin as a carrier protein" VACCINE,GB,BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 18, 1998, pages 1732-1741, XP002089380 ISSN: 0264-410X the whole document	1-5,7-9, 13-18

A	DE VELASCO E ALONSO ET AL: "Synthetic peptides representing T-cell epitopes act as carriers in pneumococcal polysaccharide conjugate vaccines." INFECTION AND IMMUNITY, vol. 63, no. 3, 1995, pages 961-968, XP002149966 ISSN: 0019-9567 the whole document	1-5, 8-11, 13-18

	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 17209 A (SMITHKLINE BEECHAM BIOLOG ;MOMIN PATRICIA MARIE (BE); GARCON NATHA) 29 June 1995 (1995-06-29) cited in the application page 4, line 26 -page 5, line 16 claims 1-5,8-10,12,13	10-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/EP 00/02467

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9006951 A	28-06-1990	AU 626961 B	13-08-1992
		AU 4756490 A	10-07-1990
		BG 51358 A	15-04-1993
		CA 2005704 A	16-06-1990
		DK 115591 A	14-08-1991
		EP 0449856 A	09-10-1991
		FI 103122 B	30-04-1999
		HU 58804 A	30-03-1992
		JP 4503948 T	16-07-1992
		MC 2178 A	22-05-1992
		NO 304317 B	30-11-1998
		RU 2121481 C	10-11-1998
WO 9633739 A	31-10-1996	AP 771 A	07-10-1999
		AT 186842 T	15-12-1999
		AU 693022 B	18-06-1998
		AU 5334596 A	18-11-1996
		AU 699213 B	26-11-1998
		AU 6987398 A	23-07-1998
		BG 101995 A	30-11-1998
		BR 9608199 A	18-05-1999
		CA 2217178 A	31-10-1996
		CN 1182370 A	20-05-1998
		CZ 9703379 A	18-03-1998
		DE 69605296 D	30-12-1999
		DE 69605296 T	18-05-2000
		EP 0822831 A	11-02-1998
		EP 0884056 A	16-12-1998
		EP 0955059 A	10-11-1999
		ES 2140076 T	16-02-2000
		GR 3031912 T	29-02-2000
		HU 9801560 A	28-10-1998
		JP 11504020 T	06-04-1999
		NO 974859 A	21-10-1997
		NZ 305365 A	28-05-1999
		PL 322968 A	02-03-1998
		SI 822831 T	29-02-2000
		SK 144297 A	06-05-1998
		ZA 9602612 A	29-08-1996
WO 9517209 A	29-06-1995	AT 177322 T	15-03-1999
		AU 1316495 A	10-07-1995
		AU 687494 B	26-02-1998
		AU 1316695 A	10-07-1995
		AU 705521 B	27-05-1999
		AU 6803198 A	09-07-1998
		AU 705519 B	27-05-1999
		AU 6803298 A	09-07-1998
		CA 2179779 A	29-06-1995
		CN 1138298 A	18-12-1996
		DE 69417063 D	15-04-1999
		DE 69417063 T	28-10-1999
		DK 735898 T	23-08-1999
		WO 9517210 A	29-06-1995
		EP 0735898 A	09-10-1996
		EP 0868918 A	07-10-1998
		ES 2129801 T	16-06-1999
		GR 3029750 T	30-06-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/EP 00/02467

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9517209 A		JP 9506887 T	08-07-1997
		NZ 277802 A	27-04-1998
		SG 49257 A	18-05-1998
		SI 735898 T	30-06-1999
		ZA 9410176 A	17-11-1995

REPLACED BY ART 34 AMDT

14

REC'D 16 MAR 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
ML/B45182		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02467	17/03/2000	19/03/1999
International Patent Classification (IPC) or national classification and IPC A61K39/09		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/10/2000	13.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Thiele, U Telephone No. +49 89 2399 8643

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02467

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-72	as originally filed				

Claims, No.:

1-15	as received on	05/03/2001	with letter of	02/03/2001	

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 12,15.

because:

   ☒ the said international application, or the said claims Nos. 12,15 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-15

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11,13,14
	No:	Claims	12?,15?(see section III)

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Section III

Claims 12 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section V

1) Reference is made to the following documents:

D1: WO 90 06951 A
D2: CRITICAL REVIEWS IN MICROBIOLOGY, vol. 23, no. 2, 1997, pages 121-141 .
D3: CLINICAL MICROBIOLOGY REVIEWS, vol. 11, no. 4, October 1998, pages 645-657
D4: INFECTION AND IMMUNITY, vol. 62, no. 12, 1994, pages 5683-5688
D5: VACCINE,GB,BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 18, 1998, pages 1732-1741
D6: WO 96 33739 A

2) The subject-matter of claim 1 would appear to be novel and inventive in view of the known state of the art (Art. 33(2), (3) PCT).

D1 (see esp. page 2, line 16 - page 4, line 23; page 10, lines 1 - 3; claims 9 - 14, claim 23) merely discloses vaccines comprising at least one Streptococcus

pneumoniae polysaccharide antigen and the S. pneumoniae protein antigen pneumolysin in a mutated form, and the preparation thereof. The polysaccharide may be derived from a poly-, esp. 23valent vaccine. Adjuvants such as alumina gel may be added. The antigen / polysaccharide complex is either conjugated or non conjugated. Carrier proteins such as tetanus toxoid are mentioned. The vaccine aims at protecting young children from pneumococcal infection.

D2 (see esp. page 132, col. 2, line 27 - page 135, col. 2, line 18) merely pertains to pneumococcal glycoconjugate vaccines. To this end, inactivated pneumolysin or pneumococcal surface protein A is conjugated to one or more pneumococcal polysaccharides. Carrier proteins such as tetanus toxoid are mentioned. The vaccine aims at protecting infants and the elderly (see page 121, r. col.).

D3 (page 646, chapter headed "Polysaccharide-Protein Conjugate [...]"; page 653, chapter headed "Potential use of PspA [...]") merely suggests in particular the use of Pneumococcal surface protein A as a carrier for pneumococcal polysaccharides in vaccines for young children and the elderly.

D4 overcomes the poor immunogenicity of (multivalent) S. pneumoniae polysaccharides in vaccines by including pneumococcal proteins, in particular pneumolysin toxoids, either as protein carrier and/or as protective immunogen in their own right (see esp. page 5683, r.col., lines 4 - 8; p. 5687, "Conclusion").

Lastly, D5 is merely concerned with detoxified pneumolysin as a carrier protein for pneumococcal capsular polysaccharides.

None of the said documents however contemplates the use of an adjuvant which is a preferential inducer of a Th1 response.

Although D6 (see pages 1, 2; claims 1, 5, 8 - 10, 12) discusses such Th1 adjuvants, there is no mention of how it could aid the coordination of humoral and cell-mediated immune responses against pneumococci when present in a composition further comprising a pneumococcal polysaccharide and protein, this being the unexpected effect resulting from the feature distinguishing the subject-matter of claim 1 from D1 - D5. D6 rather teaches that necrosis at the injection site

of vaccination can be avoided by use of formulations containing a combination of such adjuvant and a sterol.

The afore mentioned advantages of the present invention are apparent from the description, page 16, line 27 - page 17, line 6; page 60, lines 8 - 12; and Examples 4B and 4C.

3) Independent claims 10 - 15 rely on the same novel and inventive concept as claim 1 and therefore, together with dependent claims 2 - 9, also meet the requirements of Arts. 33(2) and (3) PCT.

Section VII

1) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 - D5 is not mentioned in the description, nor are these documents identified therein.

2) The description has not been adapted to the wording of the amended claims (Guidelines C-III, 4.3)

Additional note: The applicant submitted written evidence (PubMed entries with PMIDs 11115692, 10217586, 9726341 and 9674889) for a general acceptance of the said term "CRM197" in the technical field concerned.

Claims:

1. An immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen and at least one *Streptococcus pneumoniae* protein antigen or immunologically functional equivalent thereof.

2. The immunogenic composition of claim 1, wherein the protein antigen is an outer surface protein or a secreted protein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.

3. The immunogenic composition of claims 1 or 2, wherein the protein antigen is a toxin, adhesin or lipoprotein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.

4. The immunogenic composition of claims 1-3, wherein the protein antigen or immunologically functional equivalent thereof is selected from the group: pneumolysin, PspA or transmembrane deletion variants thereof, PspC or transmembrane deletion variants thereof, PsaA or transmembrane deletion variants thereof, glyceraldehyde-3-phosphate dehydrogenase, and CbpA or transmembrane deletion variants thereof.

5. The immunogenic composition of claims 1-4, wherein the polysaccharide antigen is presented in the form of a polysaccharide-protein carrier conjugate.

6. The immunogenic composition of claim 5, wherein the carrier protein is selected from the group consisting of: Diphtheria toxoid, Tetanus toxoid, CRM197, Keyhole Limpet Haemocyanin (KLH), protein derivative of Tuberculin (PPD), and protein D from *H. influenzae*.

7. An immunogenic composition as claimed in any of claims 1 to 6 wherein the vaccine comprises at least four pneumococcal polysaccharide antigens from different serotypes.

8. An immunogenic composition as claimed herein additionally comprising an adjuvant.

9. An immunogenic composition as claimed in claim 8, wherein the adjuvant comprises an aluminium salt.

10. An immunogenic composition as claimed in claim 8, wherein the adjuvant is a preferential inducer of a TH1 response.

11. An immunogenic composition as claimed in claim 10, wherein the adjuvant comprises at least one of the following: 3D-MPL, a saponin immunostimulant, or an immunostimulatory CpG oligonucleotide.

12. An immunogenic composition as claimed in claim 11, wherein the adjuvant comprises a carrier selected from the group comprising: an oil in water emulsion, liposomes, and an aluminium salt.

13. An immunogenic composition composition as claimed herein for use as a medicament.

14. A vaccine comprising the immunogenic composition of claims 1-12.

15. A method of preventing or ameliorating *Streptoccocus pneumoniae* infection in a patient over 55 years, comprising administering an effective amount of a vaccine comprising a *Streptococcus pneumoniae* polysaccharide and at least one *Streptococcus pneumoniae* protein, and optionally a TH1 inducing adjuvant.

16. Use of a pneumococcal polysaccharide antigen in combination with a *Streptoccocus pneumoniae* protein antigen, and optionally a TH1 inducing adjuvant, in the manufacture of a medicament for the prevention of pneumonia in patients over 55 years.

17. A method of making an immunogenic composition as claimed herein, comprising the steps of:

selecting one or more pneumococcal polysaccharide antigen(s);

selecting one or more pneumococcal protein antigen(s); and

mixing said polysaccharide and protein antigens with a suitable excipient.

18. A method of preventing or ameliorating Otitis media in Infants, comprising administering a safe and effective amount of a vaccine comprising a *Streptococcus pneumoniae* polysaccharide antigen and a *Streptococcus pneumoniae* protein antigen optionally with a TH1 adjuvant, to said Infant.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 39/09, 39/385, 39/39, A61P 31/04

A2

(11) International Publication Number: WO 00/56359

(43) International Publication Date: 28 September 2000 (28.09.00)

(21) International Application Number: PCT/EP00/02467

(22) International Filing Date: 17 March 2000 (17.03.00)

(30) Priority Data:

9906437.0	19 March 1999 (19.03.99)	GB
9909077.1	20 April 1999 (20.04.99)	GB
9909466.6	23 April 1999 (23.04.99)	GB
9916677.9	15 July 1999 (15.07.99)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B–1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CAPIAU, Carine [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE). DESCHAMPS, Marguerite [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE). DESMONS, Pierre, Michel [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE). LAFERRIERE, Craig, Antony, Joseph [CA/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE). POOLMAN, Jan [NL/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE). PRIEELS, Jean–Paul [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE).

(74) Agent: GIDDINGS, Peter, John; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: VACCINE

(57) Abstract

The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to vaccines comprising a pneumococcal polysaccharide antigen, typically a pneumococcal polysaccharide conjugate antigen, formulated with a protein antigen form *Streptococcus pneumoniae*, and optionally a Th1–inducing adjuvant.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		